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| EXAMINER |
|---|
| HUTSON, RICHARD G |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1652 | 11 |

DATE MAILED: 06/06/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Applicati n No. | Applicant(s) | |
|---|---|---|---|
| | 09/851,873 | KLETZIEN ET AL. | |
| | Examiner | Art Unit | |
| | Richard G Hutson | 1652 | |

*-- The MAILING DATE f this communication appears on the c ver sheet with the correspond nc address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *07 April 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-49* is/are pending in the application.

4a) Of the above claim(s) *6 and 9-49* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5,7 and 8* is/are rejected.

7)☐ Claim(s) *4* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 April 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

Applicants amendment of the specification, and claims 1-8, Paper No. 10, 4/7/2003, is acknowledged. Claims 1-49 are at issue and are present for examination.

Applicants' arguments filed on 4/7/2003, Paper No. 10, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claims 1-14 and 19-22 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, the requirement having been traversed in Paper No. 13.

Claims 6 and 9-49 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, the requirement having been traversed in Paper No. 8.

### *Claim Objections*

Claim 4 is objected to because of the following informalities:

Claim 4 is dependent on rejected claim 1.

Appropriate correction is required.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 7 remains rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The rejection was stated in the previous office action. Claim 7 is indefinite in the recitation of "stringent conditions" as the specification does not define what conditions constitute "stringent". While page 21 of the specification describes some conditions which are intended to be stringent, there is nothing to suggest that other conditions would not also be included within the scope of this term and in the art what is considered stringent varies widely depending on the individual situation as well as the person making the determination. As such it is unclear how homologous to the sequence of a polynucleotide of SEQ ID NO: 76, a sequence must be to be included within the scope of these claims.

Applicants traverse this rejection based on applicants interpretation of sections 2173.02 and 2173.04 of the MPEP. Applicants argue that "breadth of claim is not to be equated with definiteness" and that "stringent conditions" is a term of art well recognized by those of skill and given the guidance presented in the specification, applicants submit that the claim is sufficiently clear to apprise those of skill as to the scope of the claim. In response to applicants comments, it is pointed out to applicants that MPEP 2173.04 states "If the scope of the subject matter embraced by applicants is clear and if applicants have not otherwise indicated that they intend the invention to be of different scope from that defined in the claims, then the claims comply with 35 U.S.C. 112

second paragraph". This is the basis of the above rejection, the scope of the claim is not clear.

Furthermore, applicants present as support of their position a number of recently issued patents which contain language applicants consider analogous to that of instant claim 7. In response to any questions of the patentability of claims issued in the referred to patents based on the terminology used in these patents, applicants are reminded that these are separate applications/patents then the instant application and the factual pattern of the disclosures is thus different from the instant application and subject to the interpretation of the examiner's of the applications/patents in question. As this rejection is not made with respect to these referred to applications, comments on the terminology used in these applications is not considered pertinent to the instant rejection.

Further, applicants comments that applicants have used the same language as the Written Description Guidelines in which the phrase "nucleic acid that specifically hybridizes under stringent conditions" is used are acknowledged, however, applicants are reminded that the current rejection is a 112 second paragraph rejection, and the referred to example is presented for use in analysis of claims under 112 first paragraph written description, not 112 second paragraph, and thus the factual pattern as discussed above, in reference to the presented U.S. Patents is different, and thus any comment with respect to 112 second paragraph issues not considered relevant. Regardless, it is pointed out to applicants that the example to which applicant presumably refer (Example 9: Hybridization) defines "highly stringent hybridization

conditions" as 6XSSC and 65 degrees Celsius, thus defining the scope of those nucleic acids encompassed by the referred to claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 5, 7 and 8 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The rejection was stated originally in the previous office action as it applied to claims 1-3, 5, 7 and 8. In response to this rejection, applicants have amended claims 1-3, 5, 7 and 8 and traverse the rejection as it applies to the amended claims.

Applicants have amended the claims (I-3) such that each of the polypeptides of the claimed genus comprise a QACXG domain. Applicants traverse the rejection on the basis that throughout the specification applicants have provided detailed descriptions of the caspases intended to be encompassed by the claimed invention. Applicants point out that at page 1, line 18 through page 2, line 3 applicants teach that caspases are initially expressed as zymogens and that they have a pentapeptide which contains a catalytic cysteine. Applicants further submit that other domains such as the caspase-recruiting domain (CARD) and the death effector domain (DED) are also discussed and the specification provides details of caspase activities that the proteins of the claimed

invention should possess. Thus in light of these specific disclosures in the specification it is the position of applicants that those of skill in the art would have understood that applicants were in possession of the claimed invention.

Applicants further traverse the rejection on the basis that applicants have conformed to the language suggested in Example 14 of the guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, in that claim 1 identifies a sequence (i.e. SEQ ID NO: 77), claim 1 identifies the percent homology (98%) and also provides the catalytic activity and a specific catalytic cysteine residue.

Applicants point out, that as indicated in the Guidelines, this claim encompasses two different generic embodiments, the first being a protein which comprises SEQ ID NO: 77, and the second being variants of SEQ ID NO: 77, and applicants submit that the specification expressly reduces to practice the species of SEQ ID NO: 77 and various variants thereof. Applicants point out that it is not essential to provide a specific working example of all other species "since all of the variants must possess the specified catalytic activity and must have at least" 98% structural identity with the reference compound and because of the presence of various assays which applicants have provided for identifying at least 99% identical variants of SEQ ID NO: 77 that are capable of the specified caspase activity.

Applicants arguments are not found persuasive based on the following. The rejected claims are directed to all possible caspase polypeptides comprising an amino acid sequence that is at least about 98% identical to 30 contiguous amino acids

of SEQ ID NO: 77, wherein said polypeptide comprises a QACXG domain and possess caspase activity and fusion polypeptides comprising said caspase polypeptide (claims 1, 5 or 8), wherein said polypeptide is encoded by a polynucleotide that hybridizes under stringent conditions to SEQ ID NO: 76, or the non-coding strand thereof (claim 7) and those caspase polypeptides comprising at least about 20 (claim 2) or 40 (claim 3) contiguous amino acids of SEQ ID NO: 77, wherein said polypeptide comprises at least one subunit of human caspase-12 (claim 5). Moreover, the specification fails to describe any other representative species by any identifying characteristics or properties other than comprising 30 amino acids of SEQ ID NO:77 and the functionality of caspase activity. Given this lack of description of representative species encompassed by the genus of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

All the rejected claims recite polypeptides which comprise a fragment that is at least about 98% identical to 30 contiguous amino acids of SEQ ID NO: 77, comprises a QZCXG domain and has caspase activity. The recited structural feature of the genus (i.e., that is at least about 98% identical to 30 contiguous amino acids of SEQ ID NO: 77 and comprises a QZCXG domain) does not constitute a substantial portion of the genus as the remainder of the structure of a polypeptide with caspase activity is completely undefined. Fragments consisting of 30 amino acids of SEQ ID NO:77 and merely comprise a QZCXG domain are highly unlikely to have caspase activity themselves and

the specification does not define the remaining structural features necessary for members of the genus to be selected.

Applicants attention is drawn to the example pointed out by applicants (i.e. Example 14 of the Written Description Guidelines) in which the referred to claim is drawn to variants of SEQ ID NO: 3 that are 95% identical to SEQ ID NO: 3, not 98% identical to a fragment of SEQ ID NO: 3. While applicants argue that they have provided for identifying at least 99% identical variants of SEQ ID NO: 77, that are capable of caspase activity, however it remains to be seen if applicants have provided for identifying those variants that are merely 98% identical to any 30 contiguous amino acids of SEQ ID NO: 77, a 373 amino acid protein. Thus applicants genus of claimed polypeptides encompasses those polypeptides which comprise less then one tenth of the disclosed polypeptide comprising the amino acid sequence of SEQ ID NO: 77.

Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 1-3, 5, 7 and 8 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a caspase polypeptide comprising the amino acid sequence of SEQ ID NO: 79, does not reasonably provide enablement

for any caspase polypeptide comprising an amino acid sequence at least 98% identical to 30 contiguous amino acids of SEQ ID NO: 79, wherein said polypeptide comprises a QACXG domain and possesses caspase activity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The rejection was stated originally in the previous office action as it applied to claims 1-3, 5, 7 and 8. In response to this rejection, applicants have amended claims 1-3, 5, 7 and 8 and traverse the rejection as it applies to the amended claims.

Applicants traverse the rejection on the basis that the claims of the present invention are directed to novel caspase proteins, the claims recite the sequence of the claimed caspase proteins and the specification recites that the caspase proteins comprise a QACXG sequence which contains the catalytic cysteine residue present in standard caspase proteins. Applicant is reminded that the currently rejected claims do not recite the sequence of the claimed caspase proteins, but rather a subsequence of a species of the claimed caspases and the specified QACXG sequence which contains the catalytic cysteine residue is present in most if not all caspase proteins. Thus the structural limitations of the claimed genus of caspase polypeptides is such that applicants have not enabled the full scope of the genus of caspase polypeptides comprising merely 98% identity to any 30 contiguous amino acids of the 373 amino acids of SEQ ID NO: 77, wherein said polypeptide comprises a QACXG domain and possesses caspase activity.

Applicants disclosure of a comparison of the sequence of the caspase having the amino acid sequence of SEQ ID NO: 77 and the amino acid sequence of other known caspases, the presence of a regulatory CARD domain, large and small subunits and active site residues of a number of caspase isoforms, as well as strategies for cloning an active caspase-12 protein and a description select caspase variants (i.e. Example 5), while providing guidance as to how to make and use those caspases comprising the amino acid sequence of SEQ ID NO: 77, as well as some variants of SEQ ID NO: 77, does not enable the claimed genus of caspases which comprises any caspase polypeptide comprising merely 98% identity to any 30 contiguous amino acids of SEQ ID NO: 77, wherein said polypeptide comprises a QACXG domain and possesses caspase activity.

While routine experimentation is not undue, excessive routine experimentation is undue and as such the claimed genus of caspase polypeptides which encompasses any caspase comprising a mere 98% identity to any 30 contiguous amino acids of the 373 amino acid sequence of SEQ ID NO: 77 and the QACXG sequence is not enabled.

The mere disclosure of a mammalian cell expression system to show that both the wild-type and a single deltaCARD variant were activated similarily does not enable the scope of the claimed genus. A single variant is not representative of those variants encompassed by any caspase comprising a mere 98% identity to any 30 contiguous amino acids of the 373 amino acid sequence of SEQ ID NO: 77 and comprising the QACXG sequence.

Applicants arguments are not persuasive because while methods to produce variants of a known sequence such as site-specific mutagenesis, random mutagenesis, etc. are well known to the skilled artisan producing variants as claimed by applicants (i.e., merely having 98% identity to any 30 contiguous amino acids of SEQ ID NO: 79, and comprising a QACXG domain) requires that one of ordinary skill in the art know or be provided with guidance for the selection of which of the nearly infinite number of variants that have the claimed property. Without such guidance one of ordinary skill would be reduced to the necessity of producing and testing all of the virtually infinite possibilities. This would clearly constitute undue experimentation. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has not been provided in the instant specification. As previously stated the specification does not **sufficiently** establish: (A) regions of the protein structure which may be modified without effecting caspase activity; (B) the general tolerance of caspases to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue of any caspase variant of SEQ ID NO: 77, with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated

with the scope of the claims broadly including any number of amino acid modifications of a caspase comprising the amino acid sequence of SEQ ID NO: 77, wherein said caspase polypeptide comprises the amino acid sequence QACXG. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of those polypeptides having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

**Remarks**

No claim is allowed.

***Conclusion***

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G Hutson whose telephone number is (703) 308-0066. The examiner can normally be reached on 7:30 am to 4:00 pm, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on (703) 308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3014 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Richard G Hutson, Ph.D.
Primary Examiner
Art Unit 1652

rgh
June 6, 2003